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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/756,948	01/13/2004	Martin W. Brechbiel	4239-67017-01	3278

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EXAMINER	
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ART UNIT	PAPER NUMBER
1618	

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01/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/756,948	BRECHBIEL ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-33 are pending in the application. Any objections and/or rejections from previous office actions that have not been reiterated in this office action are obviated.

Specification

The amendment to the specification filed 1/18/05 is acknowledged and entered.

Response to Arguments

1. Applicant's arguments filed 12/7/07 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) in view of Li et al. (US 7,261,875B2), Brechbiel et al. (US 7,081,452B2) and further in view of Baker, Jr. et al. (US 6,471,968B1) as stated in the office action mailed 9/7/07.

4. Applicant asserts that the reference of Li et al. provides for polymeric materials formed by polymerizing N-carboxyanhydride monomers using dendrimer initiators.

5. The reference of Li et al. does disclose the synthesis of dendritic poly(amino acid) which involves the functionalization of the dendrimer with amino acid monomers via the use of dendrimer initiators. The reference of Li et al. also discloses that the dendritic poly(amino acid) of the disclosure may be functionalized Gd-DTPA-PAMAM (DAB-AM-4, DAB-AM-8, etc. column 9, lines 21-27) dendritic diagnostic (MRI) contrast agents. The instant claims comprise dendrimers and a metal chelate and do not exclude a the inclusion of poly(amino acid) chains or attachment of the metal chelate (i.e. diagnostic agent) via poly(amino acid) chains and therefore the MRI contrast agents of the disclosure encompass those of the instant claims.

6. Applicant asserts that Li et al. discloses attaching a therapeutic agent or diagnostic agent to the poly(amino acid) chains of the modified dendrimer, not to the dendrimer itself.

7. The dendrimer conjugates of the instant claims comprise a dendrimer and a metal chelate and thus do not exclude the inclusion of poly(amino acid) chains or attachment of the metal chelate (i.e. diagnostic agent) via poly(amino acid) chains.

8. Applicant asserts that Li et al. teaches away from using larger dendrimers as the base of the modified dendrimers. Applicant also asserts that table 1 of Li et al. generically lists PAMAM dendrimers of generations 0-7 but that the examples of Li et al. do not employ any dendrimer larger than generation 2.

9. Li et al. teach that dendrimers, such as DAB-AM-4, DAB-AM-32, DAB-AM-64, PAMAM generations 0-7 (including large dendrimers) may be used for the invention of the disclosure (see column 9, lines 21-27; table 1). Li et al. discloses that increased

generation dendrimer would be advantageous to allow for high loading of the therapeutic diagnostic agents and a spherical morphological structure (Li et al. column 7, lines 44-45; column 8, lines 65-66). The embodiment of the disclosure/examples of the reference of Li et al. does not need to be the preferred embodiment and need not be exemplified. It would be obvious to one ordinarily skilled in the art to utilize any of the dendrimers of Li et al.

10. Applicant asserts that the office action does not identify a recognized problem in Suga et al.

11. The reference of Li et al. provides elements, such as the use of dendrimers (i.e. PAMAM, DAB) with metal chelates to improve the loading of the metal chelate and thus provides prior art elements that when combined with method of Suga et al. to yield predictable results, such as substituting the PE-PEO of Gd-DTPA-PE-POE for the PAMAM dendrimer will increase the loading of the metal chelate improved retention of the conjugates (contrast agents) in target regions, increased solubility of water-insoluble agents and allow for reduced dose which decreases in systemic toxicity (Li et al. column 1, lines 40-45; column 2, lines 56-60; column 11, lines 32-34). The recognition of a long felt need (problem) in the prior art is only one test for obviousness as well as combining prior art elements according to known methods to yield predictable results.

12. Applicant asserts the problem identified in Li et al. is targeting, not solubility of loading and teaches away from increasing the loading of an untargeted agent.

13. One concern of the reference of Li et al. is targeting of the dendrimer conjugates of the disclosure but the dendrimer conjugates of the instant claims do not exclude

targeted dendrimer conjugates. Li et al. also discloses that the dendrimer conjugates of the disclosure may have a targeting ligand and thus does not necessarily contain a targeting ligand (column 3, line 42). Another problem addressed by Li et al. is the method for improving the solubility of a compound (i.e. metal chelate) by attaching it to a dendritic poly(amino acid) (column 4, lines 61-64). Li et al. discloses that one advantage of using the dendrimer conjugates of the disclosure is that high payloads of the metal chelates increases solubility of the water-insoluble agents and allow for reduced dose which decreases in systemic toxicity (Li et al. column 1, lines 40-45; column 2, lines 56-60; column 11, lines 32-34).

14. Applicant asserts that the cited combination does not provide a finite number of predictable solutions.

15. The reference of Li et al. teaches of DAB and PAMAM dendrimers (two types) for the dendrimer conjugates (dendrimer/metal chelates) of the disclosure. The generations of DAB and PAMAM dendrimers are prepared in a predictable manner and therefore it would be predictable to try/utilize successive generations of either dendrimer to generate the most effective and efficient (MRI) contrast agents. The reference of Suga et al. teaches of the use of Gd-DTPA derivatives for the method of MR lymphography. The disclosures of Li et al. and Suga et al. teach of the use of Gd-DTPA derivatives for the method of imaging and therefore it would be obvious to substitute one Gd-DTPA derivative for another to generate the most effective and efficient imaging agent for MR lymphography.

16. DTPA and DOTA metal chelates disclosed by Brechbiel et al. (US 7,081,452B2) are well known in the prior art and therefore the use of an alternative chelate, such as 1B4M-DTPA would be obvious to try in view of the predictable results of reducing the radiotoxicity to normal tissue (Brechbiel et al. column 2, lines 13-40). The limited number of chelates provided by Brechbiel et al. would direct one of ordinary skill in the art to utilize an alternative chelate, such as 1B4M-DTPA instead of DTPA or DOTA to reduce the radiotoxicity to normal tissue.

17. Applicant asserts that the properties of the compounds of Li et al. are quite different from the unmodified PAMAM dendrimer conjugates of the instant claims. Applicant asserts that Li et al. table 1 notes that G2-PAMAM with an ethylenediamine core has a molecular weight of 3256 and the poly(amino acid) dendrimer using an ethylenediamine core has a molecular weight of 96,460, which is over 29 times heavier than the PAMAM dendrimer.

18. The dendrimer conjugates of the instant claims comprise a dendrimer and a metal chelate and thus do not exclude the inclusion of poly(amino acid) chains or attachment of the metal chelate (i.e. diagnostic agent) via poly(amino acid) chains. The limitations of size, shape, weights of the PAMAM dendrimers of the instant claims are not provided in the claims and therefore the dendrimers of Li et al. encompass those of the instant claims.

19. Applicant asserts that the pharmacological properties of dendrimer conjugates are unpredictable and would not provide a reasonable expectation of success.

Applicant also asserts that the agents of the instant claims demonstrate unexpected superior results.

20. The reference of Li et al. teaches of DAB and PAMAM dendrimers (two types) for the dendrimer conjugates (dendrimer/metal chelates) of the disclosure and the generations of DAB and PAMAM dendrimers are prepared in a predictable manner. Li et al. also discloses that attaching the therapeutic/diagnostic agents to the dendrimers of the disclosure alters the pharmokinetics of the agents and therefore it would be predictable to try/utilize successive generations of either dendrimer to generate the most effective and efficient (MRI) contrast agents. The disclosures of Li et al. and Suga et al. teach of the use of Gd-DTPA derivatives for the method of imaging (Suga et al. teaches of the use of Gd-DTPA derivatives for the method of MR lymphography) and therefore it would be obvious to substitute one Gd-DTPA derivative for another to generate the most effective and efficient imaging agent for MR lymphography.

21. The results provided in the specification compare the dendrimer conjugates of the instant claims to that of gadomer-17, GDPM which is not the products resulting from the combination of the cited references and thus there is no comparison provided with the closest prior art.

Conclusion

No claims are allowed at this time.

22. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
December 26, 2007

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER